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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,964	06/21/2001	Ya Fang Liu	YFLU-P02-001	6742

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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,964	LIU, YA FANG	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,39,40 and 44-48* is/are pending in the application.

4a) Of the above claim(s) *45-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,39,40 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 36, 39-40, and 44-48 are pending. Applicant's have cancelled claim 43 by this Amendment, dated November 16, 2004 and added new claims 45-48.

Election/Restrictions

1. Newly submitted claims 45-48 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: treating Parkinson's disease in a mammal or preventin neuronal cell death in a mammal susceptible to or having parkinson's disease by administering kinase dead MLK2 or dominant negative SEK1 that inhibits MLK activity. The compounds of claims 36, 39-40 and 44 are inhibitors of MLKs and act at the enzyme level, while MLK and SEK1 act at the gene level.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 45-48 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

2. The information disclosure statement filed January 9, 2002 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates

that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. A cover document was filed but no listing was attached.

Response to Arguments

3. Applicant's arguments filed November 16, 2004 have been fully considered but they are not persuasive.

Rejection Under 35 U.S.C. § 112

4. The rejection of claims 36, 39-40 and 44 under 35 U.S.C. § 112 first paragraph as containing subject matter not adequately described in the specification so as to enable on skilled in the art to practice the invention is maintained. The previous 35 U.S.C. § 112 first paragraph enablement rejections are incorporated in their entirety.

Applicants argue the claims 36 and 40 have been amended to include specific compounds that inhibit MLK activity by mimicking the effect of kinase-dead MKL2, which as a mutation in its ATP binding site. Applicant's arguments are based on the "implicit description" that compounds that bind the ATP binding site of MLK, are effective to inhibit MLK activity and a journal article, which demonstrates the effect of kinase-dead MLK2 as an inhibitor of MLK activity. However, the "implicit description" is new matter (see rejection below) and does not exist in the Specification, as cited for support. It is merely one example of a point mutation and Applications do not point out in what way any additional compounds will mimic this point mutation, which changes from K to E, i.e. a positive to negative charged amino acid and a potentially substantial structural change , i.e. the length of the CH_2 chain with its terminus. Moreover, the results of this kinase dead version of MLK2 and its total loss of kinase activity of

MLK2 is only disclosed by the Specification to show that MLK-associated activity mediated neuronal degeneration in Huntingon's disease, Alzheimer's disease and excitotoxicity induced by glutamate or kainite receptor activation, i.e. since excitotoxicity is a final common pathway for neuronal loss in neurodegenerative disease as well as in acute insults, inhibition of the MLK2 activity will prevent neuronal death in these neurological conditions. See Specification pp. 33-34. There is only a hint but no real link in the Specification that glutamate-mediated excitotoxicity may be a common pathway which contribute to neuronal cell death in a wide range of neurological disorder or that inhibiting preventing or inhibiting this type of excitotoxcity will treat Parkinson's. Specification, pp. 3-5. Applicant's citation of the journal article is once again to huntintin/Huntington's disease and specifically states that "activation of MLK2-mediated signaling cascade **may be partially responsible** for neuronal loss in HD (Huntington's disease), and **an inhibitor of MLK2 may be useful** for the prevention of neuronal loss in HD." Liu, et al. Activation of MLK2-mediated Signaling Cascades by Polyglutamine-Expanded Huntingtin, The Journal of Biological Chemistry, June 23, 2000, Vol. 275, No. 25, pp. 19035-19040, specifically 19040. However, the journal article does not link Parkinson's and MLK or excitotoxicity or locing ATP binding to MLY by binding to a MLK ATP binding site for a compound to treat Parkinson's or neuronal cell death related to Parkinson's.

It is thus argued that "specific inhibitors are presented via a method of identifying inhibitors of MLK enzymes by following these procedures, inhibitors can be identified. It is urged that once inhibitors are found the disclosure teaches how they can be used to treat Parkinson's.

As previously set forth, the screening assay itself is not in contention. A screening assay only needs the possibility of finding an inhibitor to be enabled. Thousands of compounds might be unsuccessfully screened for an inhibitor yet the screen itself would still be fully enabled. That is one could practice the screen albeit unsuccessfully.

Thus, the availability of a screen is no guarantee of success in finding an inhibitor for an enzyme. It is the subject of considerable original research to provide such inhibitors. The experimentation is undue and not merely routine when the decision on which compounds to test are not guided by the disclosure. In the instant case, there is no guidance at all on the selection of suitable compounds. Assuming arguendo that Applicant's amendment were even acceptable as not new matter, there is still no guidance on suitable test compounds. Applicant does not provide any guidance in the way in which to chose the enzymes in the first place and then fails to provide any guidance the way in which any point mutations of any enzymes should be made to the ATP binding region. Applicant's only argument is that identification and use of compound that inhibit ATP binding to MLK would not require undue experimentation on the part of the ordinarily skilled artisan in view of the guidance provided in the specification of the inhibitory effect of kinase-dead MLK2 on MLK activity. However, no guidance was ever provided on how kinase-dead MLK2 was chosen. Applicant's cite to general references compounds that bind to ATP binding sites of kinases and inhibit ATP binding to the ATP binding sites are useful as inhibitors of the kinases. However, 6,162,613 discloses that kinases with mutated ATP binding regions are capable of binding inhibitory compounds of other kinases with greater affinity than the wild-type kinases, i.e. non-mutated, the wild-type kinases still have inhibitory power. Abstract. US 6,573,044 is directed to purine analogs that bind to ATP binding sites of kinases,

and more specifically to cyclin-dependent kinase (CDK) with point-specific mutations. US 6,221,00 discloses BTK inhibitors and specific ways to locate its binding pocket. It cites specific references and homologies. Each of the patents provides specific guidance and working examples. None of which are disclosed by Applicant's for the instant compounds. Thus, no inhibitor leads are provided and the screening assay constitutes a wish to know as opposed to clear guidance. This is not the basis of sound enablement.

Even assuming, *in arguendo*, that the screening assay would provide inhibitors of MLK enzymes, the disclosure does not enable the use of the putative inhibitors to treat Parkinson's so as to prevent neuronal cell death. The disclosure merely speculates that inhibitors, if they were available, could be used to treat Parkinson's. Since there are no working examples of treatment with even a model system with inhibitors of MLK enzymes, it cannot be seen how the disclosure could enable such treat *in vivo*. Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because of effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to pharmaceutically acceptable compositions and methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological response to therapeutic treatments. The instant specification is absent actual working examples of how the invention would treat an individual with Parkinson's let alone **prevent** neuronal cell death in a patient so afflicted.

5. Claims 36, 39-40 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 36 and 40 recite the limitation a compound "that blocks ATP binding to MLK by binding to a MLK ATP binding site". This is considered new matter as Applicant's references to the Specification do not appear in any way reference the ATP being site or its use as a factor in the selection of a compound for treating Parkinson's or reventng neuronal cell death in a mammal susceptible to or having Parkinson's. Applicant describe the support is "implicit." However, the closest reference is in Example 3 to the kinase dead version of MLK2 and the introduction of a point mutation to the ATP binding pocket and it possible ability to mediate neuronal degeneration in Huntington's disease, Alzheimer's disease and excitotoxicity induced byglutamate or kainite receptor activation. No link is ever established between any of these and Parkinson's. Applicant only states that inhibition of the MLK2 activity will prevent neuronal death in these, i.e. Huntington's Disease and Alzheimer's Disease, neurological conditions. See Example 3 in the Specification. There is only one reference that states "**Growing** evidence suggests that glutamate-mediated excitotoxcity **may** be a common pathway which **contributes** to neuronal cell death in a wide range of neurological disorders." Specification, Pg. 2. This statement contains numerous qualifiers and does not link them together.

Claim Rejections –35 U.S.C. § 103

6. Claims 36, 39-40 and 44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Miller, et al. (US 6,060,247).

It is argued that the reference does not teach all of the claimed features, provide a motivation to modify the teaching in the reference to make the claimed invention, and the there would be a likelihood of success in making the modification. It is urged that the '247 patent does not discloses that the claimed compounds bind to the MLK ATP binding site and thereby inhibit MLK kinase activity or the administration of the compounds as a treatment for Parkinson's disease or any other apoptosis-associated disorder. It is further urged that there is no motivation to modify the general disclosure of the '247 patent to make the claimed invention.

The'247 patent clearly refers to Parkinson's and apoptosis in col. 1 by stating that "apoptosis occurs in the course of neurodegenerative disease, such as Alzheimer's and Parkinson's Diseases, which progress over a long period of time, and in acute neurological insults, such as stroke. Understanding how apoptosis is regulated is therefore, an important step toward developing effective treatments for neurodegenerative diseases and stroke." Thus, the reference to Parkinson's in column 1 is not a casual one with respect to apoptosis as is urged in the response. Rather, Parkinson's is a neurodegenerative disease identified as having a substantive undesired apoptosis component in the course of the disease. Additionally, it is one of two specific diseases mentioned in the patent with this component. The mechanisms leading to the apoptosis are what are not understood. One of the specific purposes of the '274 patent is to identify compound that inhibit apoptosis in neurons (column 2, lines 30-48). A specific linkage to MLK and Parkinson's was not established. Nevertheless, a method of screening for suitable

compounds to treat neurodegenerative disorders using adenovirus constructs is presented. It is exemplified with a specific construct. These compounds identified by the screening method are said to decrease cell death and therefore have therapeutic value in treating neurodegenerative diseases, i.e. such as the specific neurodegenerative disease mentioned in column 1 – Parkinson's (column 7, lines 31-34) It is clearly disclosed that the screening assays can be performed with constructs for mixed lineage kinases (MLK) (column 29, line 41 to column 30, line 9). Moreover, Miller clearly states, "The following groups of adenovirus constructs can be used according to the methods of the invention" at column 29, lines 43-45. This is a clear suggestion providing ample motivation to select any of the listed constructs with a reasonable likelihood of success. A reason to select the particular MLK construct out of the list is not necessary when Miller considers all of the constructs functional equivalents. Applicant's argument that the limitation that the compound that blocks ATP binding to MLK by binding to a MLK ATP binding site is not taught is not considered probative because it is new matter.

7. Claims 36, 39-40 and 44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miller, et al. (US 6,060,247) in view of Shin-San Su (US 6,162,613) or Gray (6,573,044).

It is argued that the reference does not teach all of the claimed features, provide a motivation to modify the teaching in the reference to make the claimed invention, and the there would be a likelihood of success in making the modification. It is urged that the '247 patent does not discloses that the claimed compounds bind to the MLK ATP binding site and thereby inhibit MLK kinase activity or the administration of the compounds as a treatment for Parkinson's disease or any other apoptosis-associated disorder. It is further urged that there is no motivation to modify the general disclosure of the '247 patent to make the claimed invention.

The'247 patent clearly refers to Parkinson's and apoptosis in col. 1 by stating that "apoptosis occurs in the course of neurodegenerative disease, such as Alzheimer's and Parkinson's Diseases, which progress over a long period of time, and in acute neurological insults, such as stroke. Understanding how apoptosis is regulated is therefore, an important step toward developing effective treatments for neurodegenerative diseases and stroke." Thus, the reference to Parkinson's in column 1 is not a casual one with respect to apoptosis as is urged in the response. Rather, Parkinson's is a neurodegenerative disease identified as having a substantive undesired apoptosis component in the course of the disease. Additionally, it is one of two specific diseases mentioned in the patent with this component. The mechanisms leading to the apoptosis are what are not understood. One of the specific purposes of the '274 patent is to identify compound that inhibit apoptosis in neurons (column 2, lines 30-48). A specific linkage to MLK and Parkinson's was not established. Nevertheless, a method of screening for suitable compounds to treat neurodegenerative disorders using adenovirus constructs is presented. It is exemplified with a specific construct. These compounds identified by the screening method are said to decrease cell death and therefore have therapeutic value in treating neurodegenerative diseases, i.e. such as the specific neurodegenerative disease mentioned in column 1 – Parkinson's (column 7, lines 31-34) It is clearly disclosed that the screening assays can be performed with constructs for mixed lineage kinases (MLK) (column 29, line 41 to column 30, line 9). Moreover, Miller clearly states, "The following groups of adenovirus constructs can be used according to the methods of the invention" at column 29, lines 43-45. This is a clear suggestion providing ample motivation to select any of the listed constructs with a reasonable likelihood of

success. A reason to select the particular MLK construct out of the list is not necessary when Miller considers all of the constructs functional equivalents.

Miller, does not disclose that the claimed compounds bind to the MLK ATP binding site and thereby inhibit MLK kinase activity. Assuming arguendo that this is not new matter, Shin-San Su discloses designing inhibitors serine/threonine kinanses and tyrosine kinases that are ATP site mutant kinases take advantage of the fact that these mutant kinases are capable of binding inhibitory compounds of other kinases with greater affinity than the corresponding wild-type kinase; while Gray discloses that mutations of the ATP binding site can have a 30 fold greater affinity than the known inhibitor. Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have screened for compounds that block ATP binding to MLK by binding to a MLK ATP binding site in view of the teaching so Shin-San Su or Gray in the method of Miller because altering an inhibitor's ATP binding region for a specific kinase, such as MLK, produces a greater affinity, as specifically taught by Shin-San Su or Gray.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

February 3, 2005